AMENDMENTS TO THE SPECIFICATION

Please amend the paragraph at page 2, line 1, as follows:

The first cyanoacrylates used as tissue adhesives included the short chain cyanoacrylates, commonly referred to as ~~Super Glues™~~ SUPER GLUES™, were associated with severe acute and chronic inflammatory reactions. Subsequently, longer chain cyanoacrylates, including butyl and octyl cyanoacrylates have gained acceptance. While butyl cyanoacrylates provide effective closure of simple superficial lacerations and incisions, they are toxic when introduced into vascular areas and exhibit low tensile strength and high brittleness.

Please amend the paragraph at page 7, line 11, as follows:

Sirolimus (marketed under the tradename ~~Rapamune®~~ RAPAMUNE® by Wyeth-Ayerst, previously referred to as rapamycin) is an immunosuppressive agent suitable for use in preferred embodiments. Sirolimus is a natural macrocyclic lactone with immunosuppressive properties, approved by the FDA in 1999 for the prophylaxis of renal transplant rejection. It has been shown to block T-cell activation and smooth muscle cell proliferation. Most importantly, Sirolimus does not inhibit the endothelialization of the intima. Because of its lipophilicity, the drug penetrates cell membranes enabling intramural distribution and prolonged arterial wall penetration. Cellular uptake is enhanced by binding to the cytosolic receptor, FKBP 12, which also may enhance chronic tissue retention of the drug. Use of sirolimus in cardiac stents for the prevention of restenosis is described in Sousa JE, Costa MA, Abizaid AC, Rensing BJ, Abizaid AS, Tanajura LF, Kozuma K, Langenhove GV, Sousa AGMR, Falotico R, Jaeger I, Popma JJ, Serruys PW, "Sustained suppression of neointimal proliferation by sirolimus-eluting stents. One-year angiographic and intravascular ultrasound follow-up," *Circulation*, 2001, 104:2007-2011; and Marx SO, Marks AR, "Bench to bedside. The development of rapamycin and its application to stent restenosis," *Circulation*, 2001, 104:852-855, both of which are incorporated herein by reference in their entirety. Immunosuppresive agents other than sirolimus may also be suitable for use in preferred embodiments.

Please amend the paragraph at page 10, line 21, as follows:

Other substances that may be incorporated into the microcapsules or adhesives of preferred embodiments include various pharmacological agents, excipients, and other substances well known in the art of pharmaceutical formulations. Other pharmacological agents include, but are not limited to, antiplatelet agents, anticoagulants, ACE inhibitors, and cytotoxic agents. These other substances may include ionic and nonionic surfactants (e.g., ~~Pluronic™, Triton™~~ PLURONIC™, TRITON™), detergents (e.g., polyoxyl stearate, sodium lauryl sulfate), emulsifiers, demulsifiers, stabilizers, aqueous and oleaginous carriers (e.g., white petrolatum, isopropyl myristate, lanolin, lanolin alcohols, mineral oil, sorbitan monooleate, propylene glycol, cetylstearyl alcohol), emollients, solvents, preservatives (e.g., methylparaben, propylparaben, benzyl alcohol, ethylene diamine tetraacetate salts), thickeners (e.g., pullulin, xanthan, polyvinylpyrrolidone, carboxymethylcellulose), plasticizers (e.g., glycerol, polyethylene glycol), penetrants (e.g., azone), antioxidants (e.g., vitamin E), buffering agents, sunscreens (e.g., para-aminobenzoic acid), cosmetic agents, coloring agents, fragrances, lubricants (e.g., beeswax, mineral oil), moisturizers, drying agents (e.g., phenol, benzyl alcohol), and the like.

C3

Please amend the paragraph at page 19, line 20, as follows:

Some of the more common cyanoacrylate monomers include, but are not limited to, the ethyl, methyl, isopropyl, allyl, n-butyl, isobutyl, methoxyethyl, ethoxyethyl, and octyl esters. Cyanoacrylate adhesives are manufactured and marketed worldwide by various companies including Loctite, a Henkel Company, of Rocky Hill, CT, SAFE-T-LOC International Corporation of Lombard, IL, SUR-LOK Corporation of Walworth, WI, and Elmers Products, of Columbus, OH, the manufacturer of the well-known ~~Krazy Glue™~~ KRAZY GLUE™. The ability of cyanoacrylates to rapidly cure and bond to skin makes them particularly well suited for use as medical adhesives. Cyanoacrylate adhesives suitable for use as medical adhesives include octyl 2-cyanoacrylate marketed as ~~Dermabond™~~ DERMABOND™ topical skin adhesive by Ethicon, Inc., a Johnson & Johnson Company, of Somerville, NJ, and butyl cyanoacrylate marketed as ~~Vetbond™~~ VETBOND™ by World Precision Instruments, Inc. of Sarasota, FL.

C4

Please amend the paragraph at page 24, line 15, as follows:

C5

Water-soluble polymers of any suitable molecular weight may be used. However, it is preferred that the molecular weight is selected such that the polymer chain is approximately the same length as that of the cyanoacrylate adhesive in which it is mixed. PEG with an average molecular weight of 600 provides satisfactory performance when mixed with ~~Super Glue~~ methyl cyanoacrylate adhesive.

Please amend the paragraph at page 29, line 4, as follows:

C6

Antiseptic microcapsules containing each of the antibiotics listed above were obtained by preparing an aqueous dispersion of the antibiotic and gelatin in liquid wax with vigorous stirring at 60°C. The dispersion was observed using visible microscopy to ensure the desired particle size was achieved. The dispersion was then cooled to 5°C while continuing to stir. The dispersion was then mixed with isopropanol and filtered to obtain the microcapsules. The microcapsules were treated with formalin solution, then the solution was stored in a refrigerator for about 24 hours. The solution was filtered to separate the microcapsules, which were thoroughly dried. The resulting antibiotic microcapsules were pale yellow and spherically shaped with a diameter of about 10 to 100 μm. Surfactants such as poly(vinyl alcohol) or ~~Pluronic™ F68~~ PLURONIC™ F68 may be used to stabilize the microcapsules and to provide a suitable particle size distribution. A narrow size distribution of microcapsules with a selected mean particle size can be obtained using conventional screening methods. The stability of the dispersion of microcapsules in the adhesive is largely dependent on the particle size.

Please amend the paragraph at page 30, line 19, as follows:

C7

Microcapsules with higher entrapment efficiencies may be prepared by adding 1 volume of an aqueous solution of gatifloxacin (typically about 1 to 10 wt. %), gelatin (typically about 20 wt. %), and ~~Pluronic F68~~ PLURONIC™ F68 (available from Jinling Petroleum Chemical Co. Ltd. of China, typically present at about 1 wt. % as a stabilizer) into 8 volumes of liquid paraffin (available from Hangzhou Chemical Reagent Co. of China) with vigorous stirring at 60°C. The

solution is stirred for about 15 min or until a whitish dispersion is formed. The dispersion is cooled to about 5°C and stirred for about 10 min to induce the full gelation of gelatin solution droplets. 30mL of a cold formaldehyde acetone solution (10 wt. %) is added to the system, which is stirred for another 20 min during which time crosslinking in the microcapsules occurs. The suspension is filtered and the filtered microcapsules are washed with cold acetone. The particles are vacuum dried at 40°C for 48 hours, yielding pale yellow spherical antibiotic microcapsules with size of about 10-50 microns.

Please amend the paragraph at page 31, line 5, as follows:

Adhesive formulations including unencapsulated antibiotics were investigated. The medicaments were vacuum dried for 6 hours at room temperature in the presence of phosphorous pentoxide to remove the residual water. Direct blending of the medicaments with cyanoacrylic ester was conducted in a drying chamber protected by a high-purity nitrogen atmosphere. Agglomeration was observed when Penicillin G was mixed with ~~Super Glue~~ methyl cyanoacrylate adhesive, which may be due to initiation of the cyanoacrylate curing reaction by Penicillin. In contrast to Penicillin G, the shelf life of cyanoacrylate adhesives in the presence of Sulfanilamide was observed to be more than 24 hours. This suggests that the uncured cyanoacrylate is more sensitive to Penicillin G than Sulfanilamide.

Please amend the paragraph at page 34, line 19, as follows:

Direct mixing methyl cyanoacrylate (~~Super Glue™~~ SUPER GLUE™) with dry gatifloxacin powder leads to solidification in about 3 hours at room temperature, and the color of cyanoacrylate turns to light green, indicating that some gatifloxacin has been dissolved in the ~~Super Glue™~~ SUPER GLUE™ methyl cyanoacrylate adhesive. However, a mixture of microencapsulated gatifloxacin and ~~Super Glue~~ SUPER GLUE™ methyl cyanoacrylate adhesive exhibits superior stability. The shelf life of different cyanoacrylate adhesives containing 25 wt. % gatifloxacin microcapsules (6.7% drug load) is provided in Table 1.

Please amend Table 1 on page 34 as follows:

Table 1.

Cyanoacrylate	Methyl ester (~~Super Glue~~ SUPER GLUE™)	Ethyl ester (Adhesive 502 from Beijing Chemical and Engineering Company)	Butyl ester (Suncon Medical Adhesive from Beijing Suncon Medical Adhesive Co. Ltd.)
Shelf life (Room Temperature, about 25°C)	5 days	7 days	10 days
Shelf life (4°C)	>20 days	>30 days	>40 days

C10

Please amend the paragraph at page 37, line 13, as follows:

C11

Because the UV spectra of DSP and the extractive aqueous solution of ~~Super Glue™~~ SUPER GLUE™ methyl cyanoacrylate adhesive have overlapped absorptions at 240 nm, the release behavior of cyanoacrylate adhesives containing DSP microcapsules was studied by HPLC instead of UV spectroscopy. It was found that DSP microcapsules gradually decomposed in aqueous solution and its characteristic peak in the HPLC spectrum at a retention time of 10.7 min decreased and the peak at 14.4 min appeared and grew as the decomposition process progressed. Figure 19a shows the HPLC chromatogram of a DSP microcapsule solution prepared just before testing by HPLC, whereas Figure 19b shows the HPLC chromatogram of a DSP microcapsule solution prepared one month before testing by HPLC. The peak with a retention time of 14.4 min in Figure 19b is attributed to the decomposition product of DSP, and its area varies with storage time of the DSP aqueous solution.

Please amend the paragraph at page 37, line 25, as follows:

C12

The HPLC chromatogram of an extractive solution of solidified ~~Super Glue™~~ SUPER GLUE™ methyl cyanoacrylate adhesive film containing DSP microcapsules is shown in Figure 19c. The peak at 10.7 min is observable , indicating the release of DSP. The peak at 14.4 min is also observable, indicating that part of the DSP has decomposed during the storage of the

C12 cancel.

extractive solution.

Please amend the paragraph at page 40, line 1, as follows:

C13

The experiment data also demonstrate that mixing an amount of PEG into a cyanoacrylate adhesive can increase the release rate of medicaments in the solidified film. The mechanical strength of solidified microcapsule-containing cyanoacrylate adhesive film may be noticeably reduced if the PEG content exceeds 30 wt. %, so it is preferred that the PEG be present at a concentration of 30 wt. % or less. The burst strength test of ~~Super-Glue™~~ SUPER GLUE™ methyl cyanoacrylate adhesive containing microcapsules (20 wt. %) and PEG (20 wt. %) is satisfactory (burst strength > 350 mmHg). Typically, the mechanical strength of methyl cyanoacrylate (~~Super-Glue™~~ SUPER GLUE™) is higher than that of butyl or octyl cyanoacrylate.

Please amend the paragraph at page 40, line 9, as follows:

C14

When ~~2-cyanoacylates~~ 2-cyanoacrylates are used in medical applications, their biodegradability and the mechanism of degradation may be significant to the performance of the adhesive. The degradation rate is mainly dependent on the temperature, pH of the medium, enzyme content and length of the alkyl chains. The toxicity is largely related to the degradation rates. In general, if the degradation rate of the solidified cyanoacrylate adhesive decreased to such an extent that the products of degradation may be instantly metabolized, the adhesive may be suitable for use internally because of its low toxicity. Based on the fact that the degradation rate of poly(2-cyanoacrylate) is significantly reduced in a medium having a pH<7, a cyanoacrylate adhesive containing ascorbic acid-gelatin microcapsules may be preferred. The addition of acidic substances (Vitamin C, citric acid, and the like) into cyanoacrylate adhesives may retard their polymerization and degradation, and thus lower their toxicity such that butyl- or octyl cyanoacrylate adhesives may be able to meet the requirements of internal medical use. The addition of acidic substances to ethyl cyanoacrylate adhesive (~~Krazy-Glue™~~ KRAZY GLUE™) may also make it suitable for medical purposes such as skin wound bonding, which may decrease

C 14 cancelled

the cost of medical adhesives because cost of ethyl cyanoacrylate is much lower than that of butyl- or octyl cyanoacrylate.